

## CLAIMS

### WHAT IS CLAIMED IS:

- 1                   1.     Apparatus for detection of nucleotide hybridization  
2     comprising:
  - 3                   (a)     cell walls defining a cell for holding a sample  
4     fluid;
  - 5                   (b)     at least one working electrode mounted with an  
6     electrode surface in the cell, the electrode surface being configured for  
7     attachment to nucleotides;
  - 8                   (c)     a counter-electrode mounted in the cell at a  
9     position spaced from the working electrode and positioned to be in  
10    contact with sample fluid in the cell;
  - 11                  (d)     a high frequency signal generator connected via  
12    a directional coupler to the working electrode to apply a signal at a high  
13    frequency thereto;
  - 14                  (e)     a low frequency signal generator connected to  
15    the counter-electrode to provide a signal to the counter-electrode at a  
16    frequency lower than the high frequency signal applied to the working  
17    electrode;
  - 18                  (f)     a mixer connected via the directional coupler to  
19    the working electrode to receive a high frequency signal reflected from  
20    the working electrode and connected to the high frequency signal  
21    generator, the mixer providing an output signal that is the mix of the high  
22    frequency signal from the high frequency signal generator and the signal  
23    received through the directional coupler from the working electrode; and

24 (g) a signal detector receiving the output signal  
25 from the mixer and detecting modulation of the high frequency signal by  
26 the low frequency signal thereby indicating hybridization.

1 2. The apparatus of Claim 1 further including a reference  
2 electrode mounted in the cell spaced from the working electrode and the  
3 counter-electrode and positioned to be in contact with sample fluid in the  
4 cell, the low frequency signal generator connected to the counter-  
5 electrode through the positive input of a potentiostat having a negative  
6 input which is connected to the reference electrode.

1 3. The apparatus of Claim 1 wherein the signal detector  
2 includes a lock-in amplifier receiving the output signal from the mixer and  
3 the signal from the low frequency signal generator.

1 4. The apparatus of Claim 1 wherein the high frequency  
2 from the high frequency signal generator is about 1 MHz and the low  
3 frequency signal from the low frequency signal generator is at about  
4 1 kHz.

1 5. The apparatus of Claim 1 further including a high pass  
2 filter bias Tee connected between the directional coupler and the working  
3 electrode.

1 6. The apparatus of Claim 1 wherein there are a plurality  
2 of working electrodes mounted in the cell.

1 7. The apparatus of Claim 1 including an inlet channel  
2 extending to communication with the cell by which sample fluid may be  
3 provided to the cell, and an outlet channel extending from communication  
4 with the cell by which sample fluid may be discharged from the cell.

1                   8.     The apparatus of Claim 7 wherein the sample cell is  
2     formed in a multilayer structure having a base in which the working  
3     electrode is mounted and in which a conductor extending to the working  
4     electrode is embedded, an intermediate layer defining therein the inlet and  
5     outlet channels and peripheral walls of the cell, and a top layer having the  
6     counter-electrode embedded therein.

1                   9.     The apparatus of Claim 1 further comprising a self-  
2     assembled monolayer formed on the electrode surface of the working  
3     electrode.

1                   10.    A method of detecting hybridization of nucleotides  
2     bound to the surface of a working electrode comprising:  
3                         (a)     binding nucleotides to the surface of a working  
4     electrode within a sample cell;  
5                         (b)     applying a sample fluid into the sample cell,  
6     wherein the sample fluid may contain complements to the nucleotide  
7     bound to the working electrode;  
8                         (c)     applying a high frequency signal to the working  
9     electrode and a low frequency signal to a counter-electrode within the  
10    cell; and  
11                        (d)     detecting the signal reflected from the working  
12    electrode to determine the modulation of the high frequency signal by the  
13    low frequency signal which is thereby indicative of hybridization of the  
14    nucleotides in the sample fluid to the bound nucleotides.

1                   11.    The method of Claim 10 including forming a self-  
2     assembled monolayer on the surface of the working electrode before  
3     binding nucleotides thereto.

1                   12. The method of Claim 10 wherein the high frequency  
2 signal is at about 1 MHz and the low frequency signal is about 1 kHz.

1                   13. The method of Claim 10, wherein the working  
2 electrode comprised an electronic sensing region localized to up to 0.01  
3 mm<sup>2</sup> in area.

1                   14. A system configured to detect nucleotide  
2 hybridization, the system comprising:

3                   (a) a fluid sample cell having at least one working  
4 electrode mounted therein and a counter electrode mounted therein at a  
5 distance from the at least one working electrode;

6                   (b) a first signal generator coupled to the least one  
7 working electrode;

8                   (c) a second signal generator coupled to the  
9 counter electrode; and

10                  (d) a detector receiving a signal mix of a signal  
11 reflected from the first signal generator and a signal from the first signal  
12 generator, the detector detecting modulation in the signal mix, thereby  
13 indicating hybridization in a sample in the fluid sample cell.

1                   15. The system of Claim 14, wherein the first signal  
2 generator provides a signal of at least 1 MHz.

1                   16. The system of Claim 14, wherein the at least one  
2 working electrode comprises an electrode surface covered in gold.

1                   17. The system of claim 16, wherein the electrode surface  
2 has an area of at least 0.01 mm<sup>2</sup>.

1                   18.    The system of claim 14, wherein the at least one  
2   working electrode comprises an electrode surface covered with a self-  
3   assembled monolayer.

1                   19.    The system of Claim 14, wherein the first signal  
2   generator is coupled to the at least one working electrode by a directional  
3   coupler.

1                   20.    The system of Claim 19, further comprising a high  
2   pass filter bias Tee connected between the directional couple and the at  
3   least one working electrode.